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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/322,875	05/28/1999	AVI J. ASHKENAZI	11669.19US03	8566

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EXAMINER
DECLOUX, AMY M

ART UNIT	PAPER NUMBER
1644	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/322,875	Applicant(s) ASHKENAZI ET AL.	
	Examiner Amy M. DeCloux	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20,21,23,24 and 33-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13-18* is/are allowed.

6)☐ Claim(s) *1-10,20,21,23,24 and 33-55* is/are rejected.

7)☐ Claim(s) *11 and 12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 May 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Application/Control Number: 09/322,875

Art Unit: 1644

DETAILED ACTION

Drawings

1. New formal drawings are required in this application because of the reasons outlined in PTO FORM 948, Draftsperson's Review, attached the paper mailed 12-14-01 (Paper No. 19). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

3. Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Information Disclosure Statement

2. The information disclosure statement filed 2-26-02 (Paper No. 20) has been considered.

3. The outstanding 112 second rejection and the objection to claim 11 have been withdrawn. however, the outstanding 103 rejections have been maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

MAINTAINED Claims 1-5, 9-10, 21, 23-24, 33-34, 38-40, 42-43, 47-48 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (56 on form 1449 filed 2/10/00) in view of Campbell (U on form PTO-892 filed with the previous office action).

MAINTAINED Claims 1-10, 20-21, 23-24, 36-43, 45-48 and 50-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (56 on form 1449 filed 2/10/00) in view of Campbell (U on form PTO-892 filed with the previous office action) and Gussow et al (V on form PTO-892 filed with the previous office action).

MAINTAINED Claims 35, 44 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pan et al. (56 on form 1449 filed 2/10/00)in view of Campbell (U on form PTO-892 filed with the previous office action) as applied to Claims 1-5, 9-10, 21, 23-24, 33-34, 38-40, 42-43, 47-48 and 52-54 above, and further in view of Janeway et al (Immunobiology 4th Edition (1997).

Response to Arguments

Applicants traverse the rejections on the grounds that the Pan et al reference does not provide sufficient guidance to one skilled in the art to produce the claimed antibodies. However the examiner notes that specific statements in the references themselves which would

spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA) . Pan et al teach a receptor for the apoptosis inducing peptide TRAIL, said receptor being the same protein (DR4) encompassed by the open language of the instant claims. As noted in the previous office actions, since the recited sequence is disclosed by the instant specification on page 9 as the extracellular domain of DR4, it would be obvious to one of ordinary skill to make antibodies to the extracellular portion of DR-4 (including agonist and blocking antibodies) in view of the teachings of Campbell and Gussow to have made said antibodies. Applicants further traverse on the grounds that until such types of antibodies are made and characterized, the antibodies are not known or expected. However, given that agonist as well as antagonist antibodies can generally be made for receptor proteins, as evidenced by Patent 6,429,186, filed 9-1994, (see entire patent, especially the Abstract and Examples 10-12), it is not clear how the antibodies recited in the instant claims are unexpected.

Therefore, although applicant's arguments have been carefully considered, they are not deemed persuasive, and the rejection is maintained, essentially for the reasons of record.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 1-4, 8-9, 20-21, 23-24,33-34, 38, 42-43, 47-48 and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Ni et al (US Patent No. 6,342,363).

'363 teaches antibodies, including monoclonal antibodies, resulting from immunogens of full length DR4, and DR4 polypeptide fragments such as the ligand binding domain and the death domain and include candidate agonist and antagonists from proteins and other compounds which bind the DR4 domains, including Apo-2 ligand or TRAIL, (see entire patent, especially

the Abstract, and column 27, lines 1-11, and columns 3-4). '363 also teaches an agonist capable of increasing DR4 mediated signaling to treat a disease wherein decreased apoptosis is exhibited (see entire patent, especially column 4, lines 1-35), and teaches an antagonist capable of decreasing DR4 mediated signaling in a method for inhibiting apoptosis such as for treating a disease wherein increased apoptosis is exhibited (see entire patent, especially column 4, lines 1-35). '363 teaches that an agonist can include monoclonal antibodies directed against the DR4 polypeptide (see entire patent including column 24. lines 9-19), and that an antagonist can include monoclonal antibodies directed against the DR4 polypeptide (see entire patent including column 24, lines 20-29). '363 teaches that agonist or antagonist monoclonal antibodies to DR4 may be used to treat cancer, (see entire patent including column 28, lines 27-33) and teaches pharmaceutical compositions of said antibodies (see entire patent, including column 27, lines 30-31 and 65-67 and columns 28-29). Ni et al also teaches that the term monoclonal antibody includes the multivalent $F(ab')_2$ fragments as well as the monovalent Fab fragment, (see entire patent, especially column 26, lines 60-67).

Regarding the claims are drawn to an article of manufacture which comprises an anti-DR4 antibody, container and instructions. The intended use which is recited in the instructions, lacks a function relationship to the antibody because the container and instructions do not physically or chemically affect the chemical nature of the antibody within the article of manufacture, and furthermore, the antibody can still be used by the skilled artisan for purposes other than that the instructed in vivo or ex vivo use. Therefore the anti-DR4 antibodies which are comprised within the article of manufacture are unpatentable over the prior art anti-DR4 antibodies, because they function equally effectively with or without the container or the instructions, and accordingly no functional relationship exists between the container or instructions for use and the antibodies.

Thus the claims are addressed as being drawn to an article of manufacture comprising an antibody, a container and instructions which bear no patentable weight with regard to 102 rejections.

Therefore, the referenced teachings anticipate the claimed invention.

8. Claims 5-7, 10, 35-37, 39-41, 44-46, 49-51 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ni et al. (US Patent No. 6,342,363), in view of Gussow et al (V on form PTO-892 mailed 3-28-01) , Janeway et al (Immunobiology 4th Edition (1997) (form PTO-892 filed 12-14-01), and Pan (56 on form 1449 filed 2/10/00).

Ni et al teach as above.

Ni does not teach humanized antibody to DR4 polypeptide, nor a murine antibody, nor a chimeric antibody, nor a hybridoma that produces a monoclonal antibody, nor the specific cancers of lung or colon.

Janeway et al teaches that the problem of rapidly developing antibodies directed to antibodies from non human species used in therapy of humans can be circumvented by making immunoglobulin receptors that are encoded by human genes in rag knockout mice transgenic for

human immunoglobulin receptors encoded on YACs, (see especially page 544, first paragraph), or through humanized antibodies, (see especially page 544, second paragraph).

Gussow et al teach that virtually all monoclonal antibodies are of rodent origin, especially murine due to Kohler's and Millstein's hybridoma technology used to produce large quantities of murine monoclonal antibodies, including multivalent IgM monoclonal antibodies, with a known specificity that can be used for therapeutic and diagnostic purposes, (see pages 4-5 and 99).

Pan et al teaches that the receptor DR4 is expressed in many human tissues including colon and lung, and that normal tissues are resistant to TRAIL-DR4 apoptosis, whereas most transformed cells are sensitive to it (see entire article including the Abstract and page 815, column 3 and Figure 2).

Therefore, it would have been prima facie obvious to a person of skill in the art at the time the invention was made to have applied the teachings of Gussow and of Janeway et al regarding monoclonal antibodies to the teachings of Ni et al to obtain human antibodies and human chimeric antibodies derived from murine monoclonal Variable regions, and a kit thereof, wherein said antibodies are directed against the DR4 macromolecule as taught by Ni for use in therapy since Ni et al. teaches the use of anti DR4 antibodies in cancer treatment and since Janeway et al teaches that the problem of rapidly developing antibodies directed to antibodies from non human species used in therapy of humans can be circumvented by making human immunoglobulin receptors that are encoded by human genes in rag knockout mice transgenic for human immunoglobulin receptors encoded on YACs or by making chimeric humanized antibodies using murine derived V regions recombined in a human antibody framework structure. Claims encompassing lung and colon cancer are included given the tissue distribution of DR4 taught by Pan et al. since Pan et al teaches that most transformed cells are sensitive to TRAIL-DR4 apoptosis.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

9. Claims 13-18 appear to contain allowable subject matter.

Claims 1, 11-12, 33, 42 and 47 are objected to because it is noted that the instant claims recite "...DR4 polypeptide comprising amino acid residues 24-218 of Figure 1 (SEQ ID NO:1).". However, it is noted that SEQ ID NO:1 is a nucleic acid sequence; perhaps SEQ ID NO:2 would be more appropriate since SEQ ID NO:2 is an amino acid sequence encoded by SEQ ID NO:1.

10. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 2-26-02 (Paper No.20) prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Amy DeCloux, Ph.D.
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September 5, 2002,

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